

DMB

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Display Date 5-13-02  
Publication Date 5-14-02  
Certifier A. Corbin

[Docket No. 01P-0061]

**Determination That IFEX (Ifosfamide for Injection), 1-Gram and 3-Gram Vials, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

---

**SUMMARY:** The Food and Drug Administration (FDA) is announcing its determination that IFEX (ifosfamide for injection), 1 gram (g) and 3 g, was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for ifosfamide.

**FOR FURTHER INFORMATION CONTACT:** Mitchell Weitzman, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5670.

**SUPPLEMENTARY INFORMATION:** In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

cd01155

N-1

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products with Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.” Under FDA’s regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

IFEX is the subject of NDA 19–763, held by Bristol-Myers Squibb Co. (BMS). FDA approved NDA 19–763 on December 30, 1988. Used in combination with other approved antineoplastic agents, IFEX is indicated for third line chemotherapy of germ cell testicular cancer. In the IFEX clinical studies, it was observed that urotoxic side effects, especially hemorrhagic cystitis, were frequently associated with the administration of IFEX. The approved labeling for IFEX stated that IFEX “should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna.” FDA separately approved BMS’s NDA for MESNEX (mesna) Injection on December 30, 1988. BMS never marketed IFEX alone; instead, it elected to market IFEX exclusively in a combination package with MESNEX.

IFEX as a single agent is currently listed in the “Discontinued Drug Product List” section of the Orange Book. IFEX is also listed as part of a copackaged kit with MESNEX in the Orange Book’s prescription drug product list. The relocation of IFEX as a single agent to the “Discontinued Drug Product List” coincided with a labeling modification on October 10, 1992, to reflect changes in storage conditions for IFEX and an approval of copackaging with MESNEX.

On January 31, 2001, Tom Stothoff submitted a citizen petition (Docket No. 01P-0061/CP1) to FDA under 21 CFR 10.30, requesting that the agency determine whether IFEX (as a single agent) was withdrawn from sale for reasons of safety or effectiveness. The petitioner seeks this determination in preparation for filing an ANDA for Ifosfamide for Injection, U.S.P.

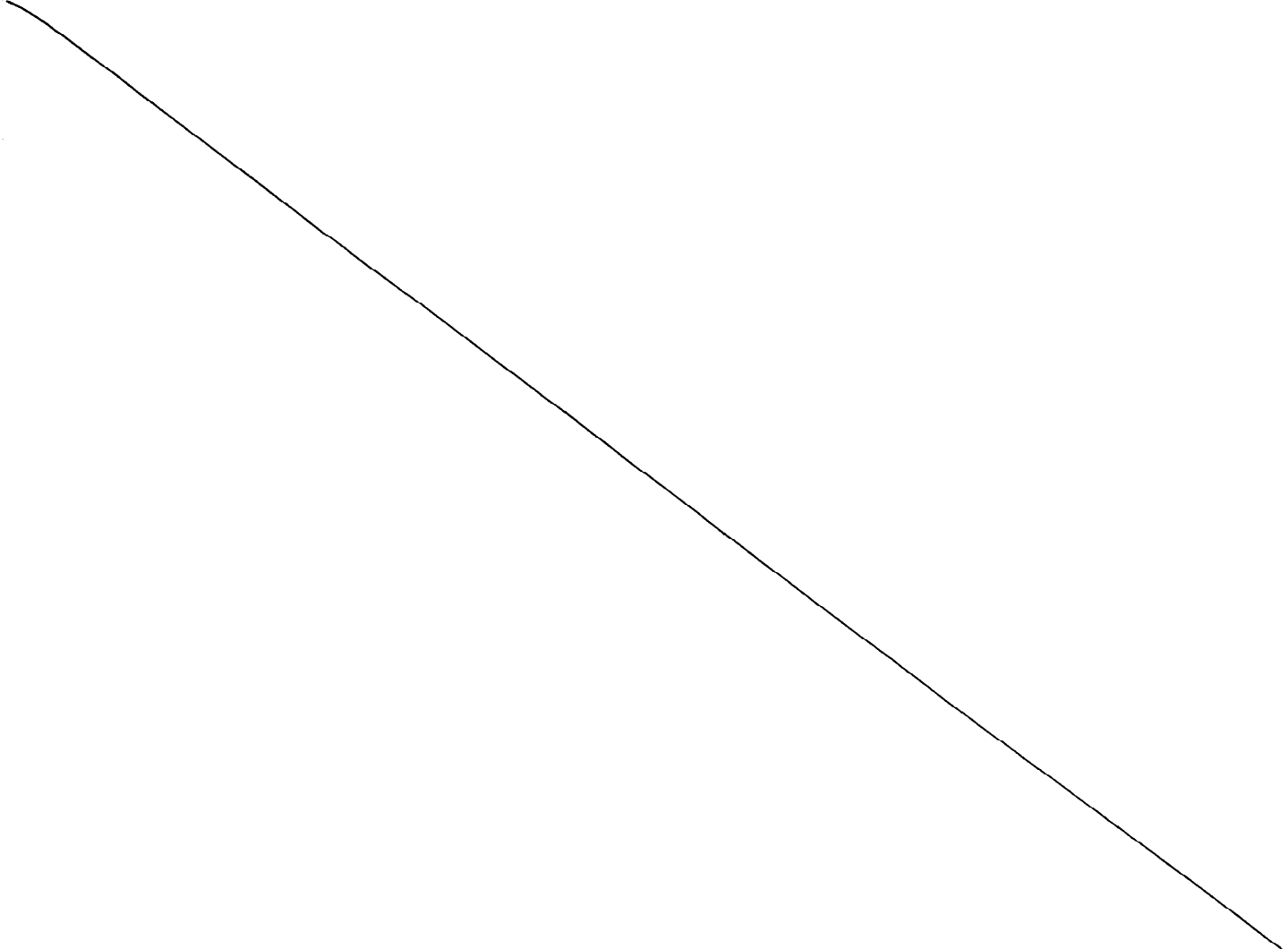
On March 9, 2001, BMS filed a comment to the citizen petition requesting that FDA find that IFEX has not been withdrawn from sale and is not separately marketed by BMS for reasons of safety or effectiveness. With respect to safety and effectiveness, BMS argued that regardless of whether IFEX was withdrawn, FDA should deny the petitioner permission to file an ANDA for ifosfamide as a single agent because, as stated in the label, ifosfamide can only be administered safely in conjunction with a uroprotective agent such as mesna. BMS cited both the medical literature and the potential for urotoxic reactions if ifosfamide is used alone in support of this claim.

BMS contends that it has never withdrawn or ceased to market IFEX because it has marketed IFEX in a combination package with MESNEX since the time of their approval. However, IFEX was approved under its own NDA as a single agent. In previous instances (see, e.g., 61 FR 25497, May 21, 1996) (addressing a relisting request for glyburide tablets), FDA has concluded that never marketing an approved product is equivalent to withdrawing the drug from sale. Therefore, even though BMS has never marketed IFEX alone, it is appropriate to categorize IFEX (as a single agent) as having been withdrawn from sale. Once a listed drug has been withdrawn from sale, FDA must make a determination that the withdrawal from sale was not for reasons of safety or effectiveness before it can approve any ANDAs referencing the listed drug.

The agency has determined that IFEX as a single agent has not been withdrawn for reasons of safety or effectiveness. FDA agrees with BMS that ifosfamide should be used with a uroprotective agent like mesna. However, that does not preclude the safe use of ifosfamide as a single agent with MESNEX or a generic version of mesna. FDA approved two ANDAs for mesna in April 2001. The FDA has no requirement that coadministered products must also be

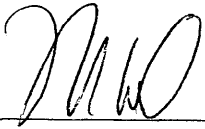
copackaged. There are many drugs whose labeling identifies them for use in combination with other drugs with which they are not copackaged, including Taxol and Taxotere. Neither the petitioner nor BMS identified any data suggesting that marketing IFEX alone would compromise patients' safety. Moreover, the relevant literature and adverse event reports do not bear out BMS's claim that marketing IFEX as a single agent would be unsafe. In the absence of data suggesting a safety risk, and because IFEX was approved as a single agent, we conclude that FDA may approve ANDAs referencing IFEX alone.

After considering the citizen petition and the comments thereon and reviewing its records, FDA determines that, for the reasons outlined previously in this document, IFEX as a single agent was not withdrawn for reasons of safety or effectiveness. Accordingly, the agency will continue to list IFEX in the "Discontinued Drug Product List" section of the Orange Book. The



"Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to IFEX, 1-g and 3-g vials, may be approved by the agency.

Dated: 5/6/02  
May 6, 2002.



Margaret M. Dotzel,  
Associate Commissioner for Policy.

[FR Doc. 02-????? Filed ??-??-02; 8:45 am]

BILLING CODE 4160-01-S

**CERTIFIED TO BE A TRUE  
COPY OF THE ORIGINAL**

